

# Chapter 5

## Bioimpedance measurements in hemodialysis patients and relation with clinical state

### 5.1 Introduction

In hemodialysis (HD), dry weight is defined as the ideal weight at the end of the hemodialysis session with normal blood pressure and without oedema. Uremic patients, regardless of whether they are undergoing renal substitutive treatment in hemodialysis (HD) or peritoneal dialysis (PD), show a continuous variation in the hydration state, which is difficult to interpret. They also display a reduction in fat free mass (FFM) and fat mass (FAT), accompanied by hypertension and cardiovascular risk with a high index of morbidity-mortality.

Mainly two bioimpedance methods are used in HD: multifrequency, based in the Cole-Cole model and monofrequency, normally using the BIVA method to analyze fluid distribution and nutritional state in HD patients. The BIVA method offers a combined assessment of hydration and nutritional state within one graph. It does not, however, provide an absolute number for dry weight (Piccoli et al 1996, 1998).

The aim of this study is to demonstrate the usefulness of the bioimpedance techniques to classify patients by their hydration and nutrition state. We made multifrequency and monofrequency (50 kHz) measurements.

### 5.2 Subject and Methods

#### 5.2.1 Patients

Measurements were taken at the Service of Nephrology of the Saturnino Lora Provincial University Hospital in Santiago de Cuba between January 2000 and November 2002. The patients were classified, a priori, as either stable (without oedema) or critical (hyperhydrated, with oedema and malnutrition) by clinical inspection. The hospital medical team made this classification and the follow up of patients for this study was concluded in October 2003. Bioimpedance measurements were taken before and after HD sessions.

### 5.2.2 Bioimpedance measurement protocol

The measurement configuration was the standard distal BIA configuration to whole-body (or hand-foot) (Grimnes and Martinsen 2000) with the patient in supine decubitus position. Four electrodes: two current injectors I, and two voltage sensor V, were dorsally placed on the right hand in the third metacarpo-phalangeal articulation and in the carpus, respectively, 5 cm apart. The pair on the foot was located in the third metatarso-phalangeal and in the articulation, 6 cm apart (Figure 4.2). We used disposable pre-gelled Ag/AgCl electrodes (3M Red Dot, Canada). The right-side measurement is appropriate because in HD sessions the right side is free of vascular accesses.

We used the impedance analyzer model BioScan: BL-960141 (Biologica, Barcelona, Spain) (Figure 4.3). This system has been validated in comparison to other bioimpedance analyzer (RJL-System) by Bland-Altman methods (Bland & Altman 1986, 1999), for more details see previous chapter. Measurement errors are lower than  $1 \Omega$  and  $1^\circ$  at 50 kHz using electrical models. Injected current has a level of 800  $\mu\text{A}$ . A frequency of 50 kHz was selected because this is the standard frequency used for BIA and BIVA (Ellis 2000, Grimnes & Martinsen 2000, Piccoli et al 1994). At 50 kHz the phase angle has a maximum in healthy people, producing a reactive component ( $X_c$ ) close also to a maximum.

### 5.2.3 Statistical analysis

The hypothesis of this study is that BIVA is an accurate method for identifying which HD patients exhibit oedema and, in some cases, malnutrition. These patients had worse prognoses for survival due to hypertension, acute lung oedema and a higher cardiovascular risk than those with more controlled hydration. With this work hypothesis, we compared BIVA results with the clinical diagnostic. We considered as our null hypothesis ( $H_0$ ) that both groups of patients, stable and critical, were extracted from the same population. Statistical significance was set at  $P < 0.05$ . In order to compare the differences between  $R/H$  and  $X_c/H$  parameters, we used Student's t test, and to compare the complex  $Z/H$  vector, we used Hotelling's  $T^2$  test (Hotelling 1947, Lentner 1982, Morrison 1967). The number of patients measured before HD was 74 (46 stable, 28 critical). After HD, we measured a subset of only 40 patients (21 stable and 19 critical). The data was analysed in comparison to the tolerance ellipses using the BIVA method. The BIVA software is based on a bivariate Hotelling's analysis (Piccoli, Pastori, BIVA software, 2002-b), for which the 95% confidence ellipse and the 50%, 75% and 95% tolerance ellipses have been extracted for the Cuban reference population using the  $RX_c$  graph.

## 5.3 Results

### 5.3.1 Multifrequency measurements

Previously, we analyzed the bioimpedance parameters (R, X<sub>c</sub>, Z and PA) at multifrequency (1, 5, 10, 50, 100, 225 kHz) in a sample of 42 patients (26: M-16 F, 30-60 yr, 1.50-1.60 m) undergoing HD session, before hemodialysis (BHD) and after hemodialysis (AHD).

The Tables 5.1 and 5.2 show the change in the bioimpedance parameters before and after HD (Nescolarde et al 2001).

**Table 5.1-** Bioimpedance parameter BHD in a sample of 42 patients with  $63.3 \pm 10.4$  kg and  $23.2 \pm 5.3$  of BMI before HD session

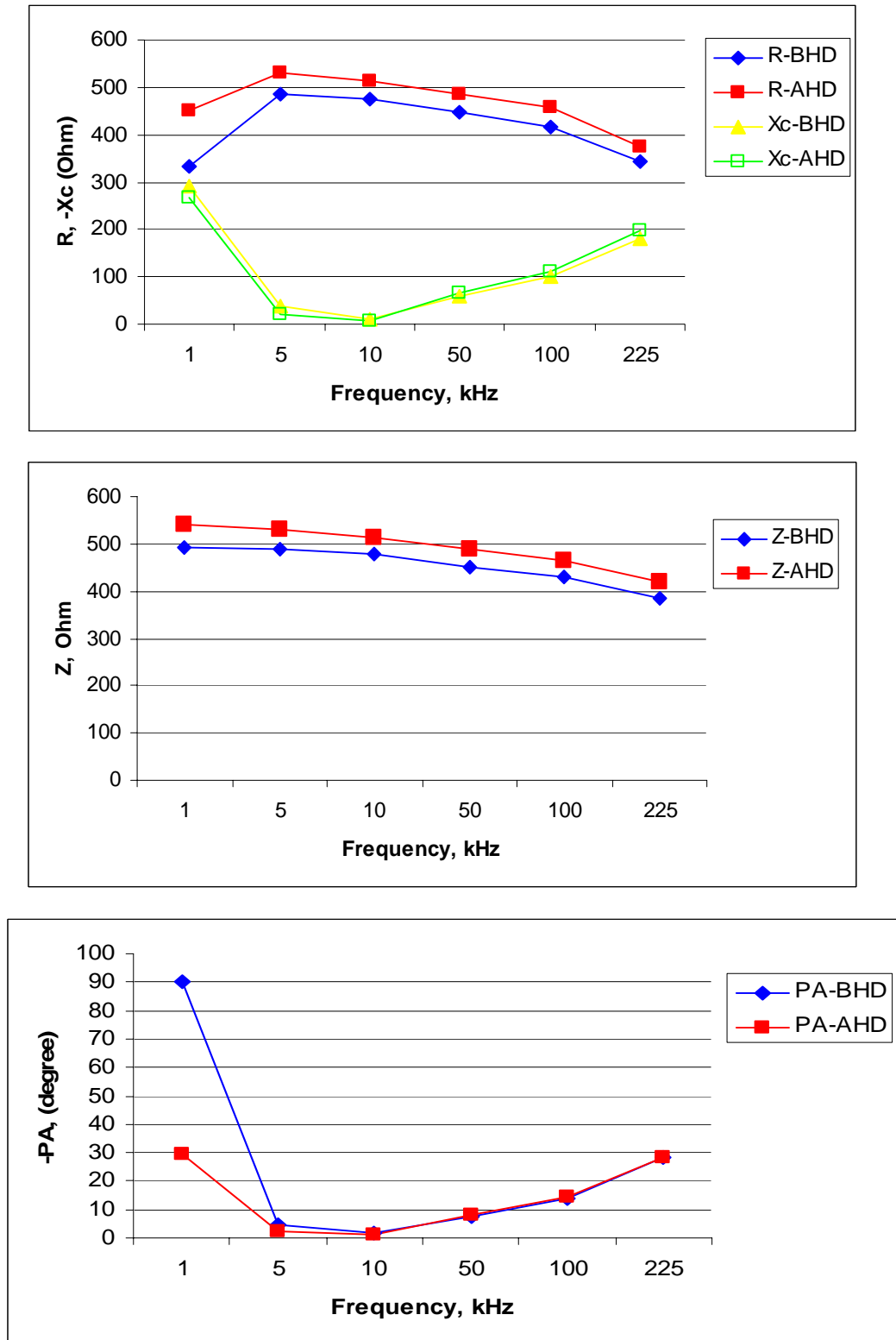
F(KHz)	R ( $\Omega$ ) Mean $\pm$ SD	-X <sub>c</sub> ( $\Omega$ ) Mean $\pm$ SD	Z ( $\Omega$ ) Mean $\pm$ SD	-PA( $^\circ$ ) Mean $\pm$ SD
1	334.2 $\pm$ 63.7	292.5 $\pm$ 36.4	492.6 $\pm$ 86.6	90.3 $\pm$ 3.2
5	487.1 $\pm$ 83.4	37.8 $\pm$ 9.8	489.9 $\pm$ 84.4	4.4 $\pm$ 0.8
10	476.2 $\pm$ 96.5	9.9 $\pm$ 22.8	476.9 $\pm$ 96.7	1.6 $\pm$ 0.4
50	446.9 $\pm$ 66.5	57.2 $\pm$ 10.9	450.6 $\pm$ 94.3	7.6 $\pm$ 0.6
100	417.5 $\pm$ 87.3	100.6 $\pm$ 20.8	429.4 $\pm$ 89.6	14.1 $\pm$ 0.8
225	342.1 $\pm$ 73.5	178.9 $\pm$ 32.6	386.4 $\pm$ 79.7	28.3 $\pm$ 1.3

**Table 5.2-** Bioimpedance parameter AHD in a sample of 42 patients with  $61.0 \pm 13.1$  kg and  $22.7 \pm 5.2$  of BMI after HD session

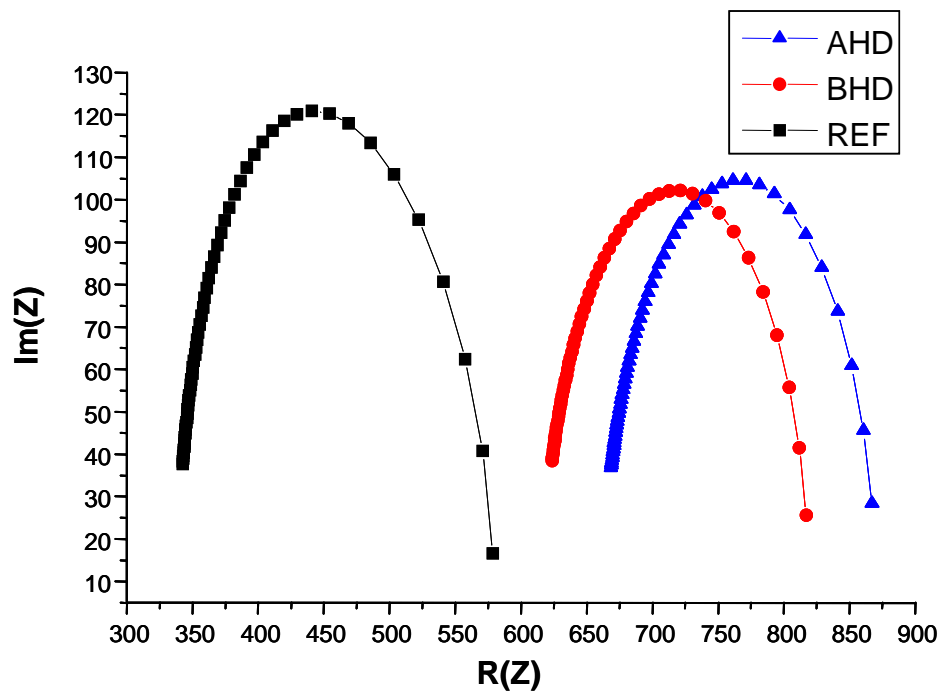
F(KHz)	R ( $\Omega$ ) Mean $\pm$ SD	-X <sub>c</sub> ( $\Omega$ ) Mean $\pm$ SD	Z ( $\Omega$ ) Mean $\pm$ SD	-PA( $^\circ$ ) Mean $\pm$ SD
1	449.8 $\pm$ 63.2	268.4 $\pm$ 35.9	542.6 $\pm$ 85.9	29.8 $\pm$ 3.2
5	530.1 $\pm$ 83.1	30.7 $\pm$ 9.6	530.5 $\pm$ 85.9	2.4 $\pm$ 0.5
10	512.7 $\pm$ 96.3	6.8 $\pm$ 22.4	512.7 $\pm$ 96.7	1.1 $\pm$ 0.5
50	485.8 $\pm$ 63.7	64.4 $\pm$ 11.5	489.6 $\pm$ 96.3	7.9 $\pm$ 0.7
100	457.2 $\pm$ 86.2	111.1 $\pm$ 21.4	464.6 $\pm$ 89.1	14.2 $\pm$ 0.8
225	372.9 $\pm$ 72.6	196.1 $\pm$ 33.2	420.8 $\pm$ 78.6	28.2 $\pm$ 1.3

Figure 5.1 shows our results, the ones in figure 5.2 plus a reference sample (Nescolarde et al 2001-a, 2001-b), excluding the measurements at 1 kHz and 5 kHz. Only measurements between 10 kHz and 225 kHz were used, all the impedances at other frequencies were extrapolated.

using mathematical fitting (Nescolarde et al 2001-a). The Cole-Cole arc for a reference (healthy) sample and for patients BHD and AHD show similar compartment compared to results obtained by Cornish et al (1994 and 1996).



**Figure 5.1-** Mean value of multi-frequency bioimpedance parameters (R and Xc, Z, PA) before BHD and after AHD session



**Figure 5.2-** Cole-Cole arc of reference (healthy) sample REF and patients before BHD and after AHD session (Nescolarde et al 2001-a).

In the next section, the BIVA method is used in a sample of hemodialysis patients in stable (normo-hydrated) and critical (hyperhydrated and malnutrition) states, in order to establish the relation between hyperhydration (oedema) and mortality.

### 5.3.2 Vectorial impedance

Table 5.3 and Table 5.4 show a comparison between both samples of patients—stable (without oedema) and critical (with oedema) before and after HD respectively. The bioelectrical parameters (R/H, Xc/H, PA), BMI, H and W are shown.

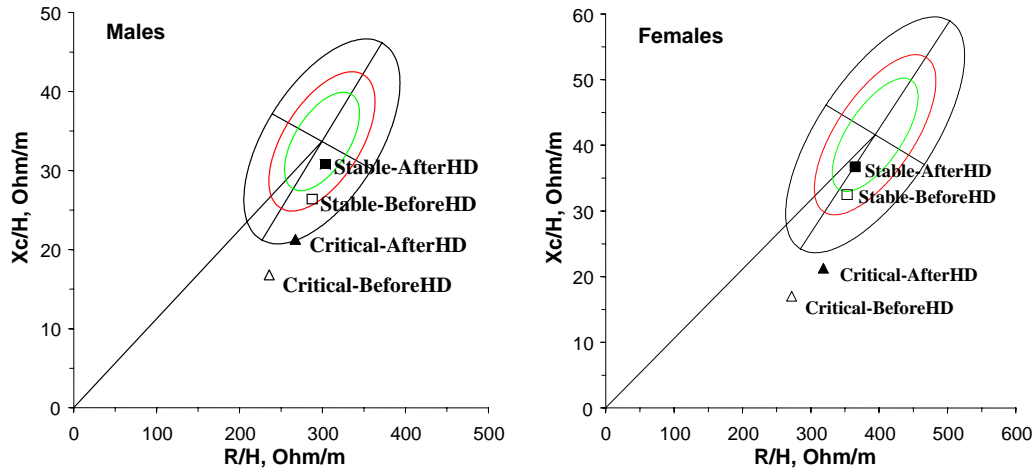
**Table 5.3-** Impedance vector components in a sample of 74 Cuban patients, before HD session: 46 stable patients (28 men, 18 women) and 28 critical patients (16 men, 12 women)

	Male		Female	
	Stable 19 ≤ BMI < 30 age 18-70	Critical 20 ≤ BMI < 22 age 18-70	Stable 19 ≤ BMI < 30 age 18-70	Critical 20 ≤ BMI < 22 age 18-70
<b>Size, N</b>	<b>28</b>	<b>16</b>	<b>18</b>	<b>12</b>
<b>BMI, kg/m<sup>2</sup></b>				
<i>Men</i>	23.1	22.5	25.0	22.2
<i>SD</i>	3.9	4.9	7.8	2.4
<b>Weight, kg</b>				
<i>Mean</i>	63.3	65.1	59.2	53.7
<i>SD</i>	10.4	15.7	17.2	7.1
<b>Height, cm</b>				
<i>Mean</i>	165.9	169.9	154.7	154.6
<i>SD</i>	13.0	6.0	9.6	5.0
<b>R/H, Ω/m</b>				
<i>Mean</i>	289.1	244.8	355.5	283.5
<i>SD</i>	40.7	45.5	74.9	43.9
<b>-Xc/H, Ω/m</b>				
<i>Mean</i>	26.6	17.7	32.8	17.9
<i>SD</i>	6.5	4.8	9.1	2.6
<b>r(R/H, Xc/H)</b>	0.9	0.8	0.9	0.7
<b>-PA, °</b>				
<i>Mean</i>	5.2	4.1	5.2	3.7
<i>SD</i>	0.8	0.8	0.7	0.4

**Table 5.4-** Impedance vector components in a sample of 40 patients after HD session: 21 stable patients (15 men, 6 women) and 19 critical patients (10 men, 9 women)

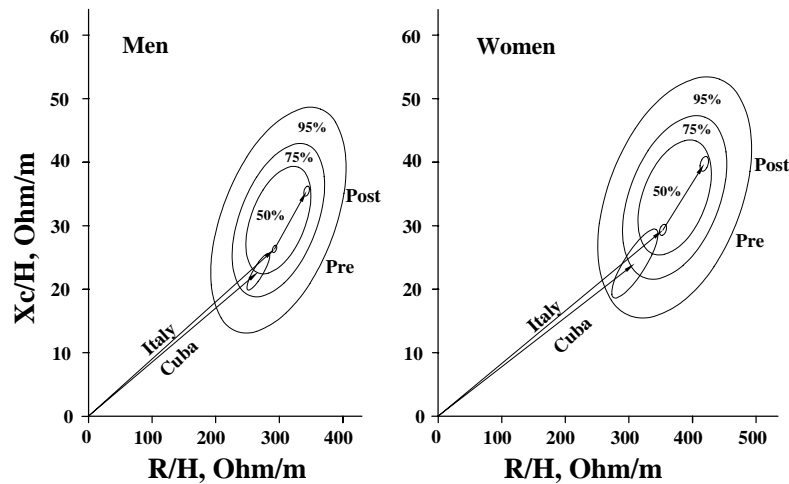
	Male		Female	
	Stable 19 ≤ BMI < 30 age 18-70	Critical 20 ≤ BMI < 22 age 18-70	Stable 19 ≤ BMI < 30 age 18-70	Critical 20 ≤ BMI < 22 age 18-70
<b>Size, N</b>	<b>15</b>	<b>10</b>	<b>6</b>	<b>9</b>
<b>BMI, kg/m<sup>2</sup></b>				
<i>Men</i>	22.7	20.7	27.5	22.2
<i>SD</i>	3.6	2.8	8.0	2.1
<b>Weight, kg</b>				
<i>Mean</i>	64.6	57.3	69.1	49.9
<i>SD</i>	12.4	8.8	21.5	3.7
<b>Height, cm</b>				
<i>Mean</i>	168.5	166.5	158.5	153.2
<i>SD</i>	12.4	7.1	6.5	3.0
<b>R/H, Ω/m</b>				
<i>Mean</i>	303.5	264.5	366.2	332.4
<i>SD</i>	51.1	28.2	63.5	55.2
<b>-Xc/H, Ω/m</b>				
<i>Mean</i>	30.1	21.4	37.0	21.5
<i>SD</i>	9.1	3.3	12.2	6.1
<b>r(R/H, Xc/H)</b>	0.8	0.6	0.9	0.8
<b>-PA, °</b>				
<i>Mean</i>	5.6	4.7	5.7	3.6
<i>SD</i>	1.2	0.8	1.2	0.7

Figure 5.3 shows the displacement for the mean Z/H vectors of each groups of Cuban patients (separated by gender) before and after the HD session in the 50%, 75%, and 95% tolerance ellipses for the Cuban reference population (Nescolarde et al 2004-a) (Figure 4.5).



**Figure 5.3-**Mean RXc values for patients before HD and after HD compared with the tolerance ellipses (50%, 75%, and 95%) for the Cuban reference population

In previous studies, we also analyzed the displacement of the impedance vector due to the HD session in order to verify that the Z/H vectors had a similar trajectory in comparison to other studies (Piccoli et al. 1994, 1996, 1998, 2002). For this analysis, we only measured a subset of 40 patients (Figure 5.4).



**Figure 5.4-**Mean impedance vectors with 95% confidence ellipse in pre-HD condition (Cuban patients) and pre-post condition (Italian patients)

## 5.3.3 Statistical analysis before HD

In Table 5.5 and 5.6 the results before HD of the Student's t test and Hotelling's  $T^2$  test for both patient groups, stable and critical: 30 women patients (18 stable, 12 critical), and 44 men patients (28 stable, 16 critical) are classified by gender. In Figure 5.5 we can see, through Z-Score (the 50%, 75% and 95% tolerances ellipses for the standard reference RXc-score graph) the differences between the Z/H vectors.

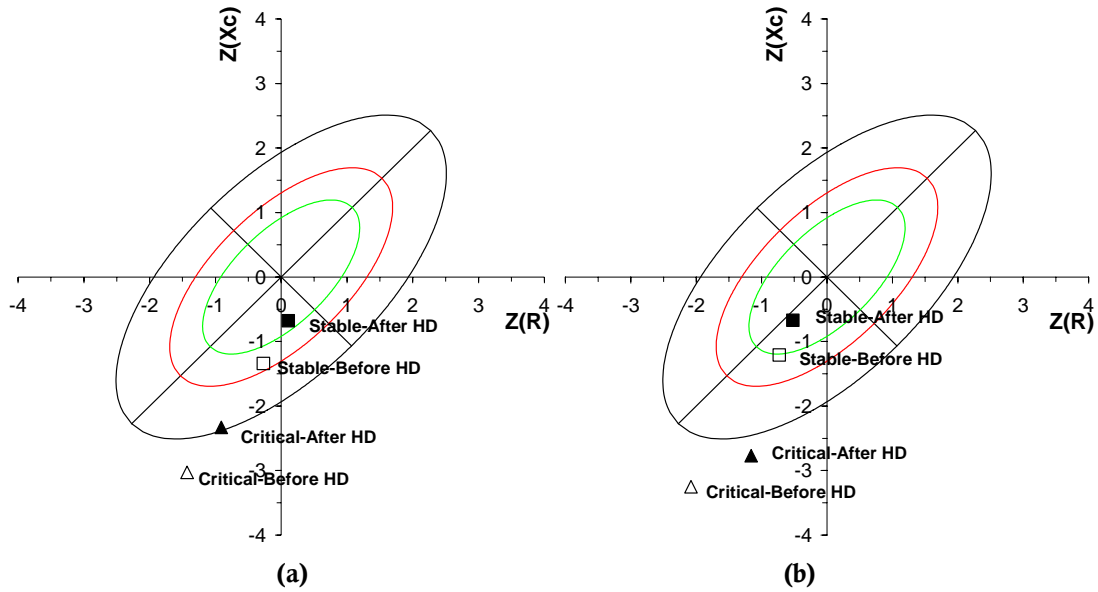
**Table 5.5-** Student's t test in a sample of 30 women patients before HD (18 stable, 12 critical), and in a sample of 44 men patients before HD (28 stable, 16 critical)

		Size, N	R/H, $\Omega/m$ Mean SD	-Xc/H, $\Omega/m$ Mean SD	r(R/H, Xc/H)	-PA, ° Mean SD
Male	Stable 19 ≤ BMI < 30 age 18-70	28	289.1 40.7	26.6 6.5	0.9	5.2 0.8
	Critical 20 ≤ BMI < 22 age 18-70	16	244.8 45.5	17.7 4.8	0.8	4.1 0.8
P (bilateral)			<b>0.001</b>	<b>0.000</b>		<b>0.000</b>
Female	Stable 19 ≤ BMI < 30 age 18-70	18	355.5 74.9	32.8 9.1	0.9	5.2 0.7
	Critical 20 ≤ BMI < 22 age 18-70	12	283.5 43.9	17.9 2.6	0.7	3.7 0.4
P (bilateral)			<b>0.002</b>	<b>0.000</b>		<b>0.000</b>

**Table 5.6-** Hotelling's  $T^2$  test in a sample of 30 women patients before HD (18 stable, 12 critical), and in a sample of 44 men patients before HD (28 stable, 16 critical)

Women Z/H(R/H, Xc/H)			Men Z/H(R/H, Xc/H)		
R/H SDx	-Xc/H SDy	r(YX)	R/H SDx	-Xc/H SDy	r(YX)
42.5	5.9	0.8	64.5	7.3	0.8
<b>P &lt; 0.05</b>			<b>P &lt; 0.05</b>		

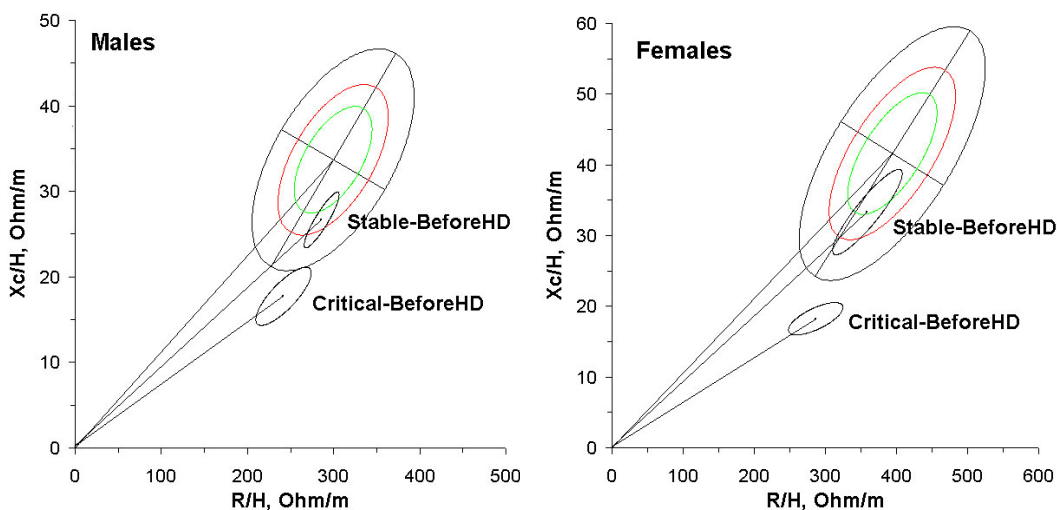




**Figure 5.5-** Stable and critical patients BHD and AHD (95% confidence interval) in Z-score of the standard, reference RXc-score graph: (a) male sample (b) female sample

### 5.3.4 Confidence ellipses before HD

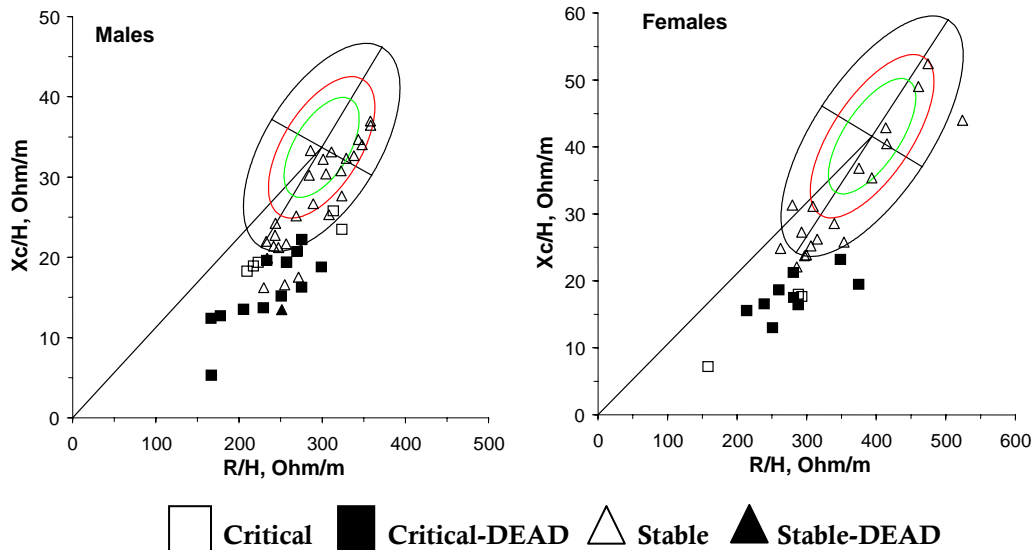
Through the 95% confidence ellipse, Figure 5.6 shows the Z/H vector differences between both groups (separated by gender) more clearly. Separate 95% confidence ellipses of mean vectors indicate a statistically significant difference in vector positions on the RXc graph, which is equivalent ( $P < 0.05$ ) to Hotelling's  $T^2$  for unpaired data (Piccoli, Pastori, BIVA software 2002-b).



**Figure 5.6-** The 95% confidence ellipses in 74 patients before HD session for 46 stable patients (28 men, 18 women), and 28 critical patients (16 men, 12 women)

### 5.3.5 Individual Z/H vector in tolerance ellipses.

Figure 5.7 shows individual bioimpedance vectors (Z/H) for each patient in comparison with the tolerance ellipses of the reference population.



**Figure 5.7-** Individual vectors for 28 critical patients (9 dead women and 11 dead men) and 46 stable patients (0 dead women and 1 dead man) in the tolerance ellipses for the reference population

## 5.4 Discussion

The Cole-Cole model has been developed for muscle cells and does not take into account the interface between electrodes and skin, or the subcutaneous tissue consisting of fat and small vessels (Kuhlman et al 2005). The problem with multifrequency analyzers is that errors at low and high frequencies are bigger than at medium frequencies i.e. 50 kHz. In the multifrequency measurements, the high values of phase angle at low frequency BHD and AHD, especially at 1 kHz, but also at 5 kHz, are not theoretically realistic (see table 5.1, 5.2 and figure 5.1). This error could be introduced due to high electrode impedance, the anisotropy of muscle tissue (Piccoli et al 2005), and limitations on the bioimpedance analyzer (at frequencies below 50 kHz the injected current is much lower due to safety reason).

In Piccoli et al (1994, 1999-a) variations in hydration, without an alteration of tissue mass-structure, are associated with a shortening (hyperhydrated-anasarca) or an enlargement (dehydration) of the vector in the greater axis direction of the tolerance ellipses. On the other hand, variations in the structure of soft tissue are associated with a migration of the vector in the small axis direction of the ellipses, with either an increase in the phase angle (obese, athletic) or a decrease in it (malnutrition-cachectic, anorexic). Advantages and

applications of the RXc-graph with BIVA method in hemodialysis are shown in Piccoli et al 1994-a, 1994-b, 1996, 1997, 1999-a, 1998-b, 2002-a, 2002-b, 2002-c, 2004-a, 2004-b, 2005-b, Kulhman et al 2005.

In our research, we observed combined variations of hydration and nutrition associated with migration of the vector, in the direction of the combination of the two principal directions (abscise R/H and ordinate  $X_c/H$ ). There is a change in both components of Z/H vector (R/H,  $X_c/H$ ) and not of one of them (Piccoli et al 1999-b). The displacement for the mean Z/H vectors in both groups of Cuban patients (separated by gender) before and after the HD session is clearly represented in Figure 5.3.

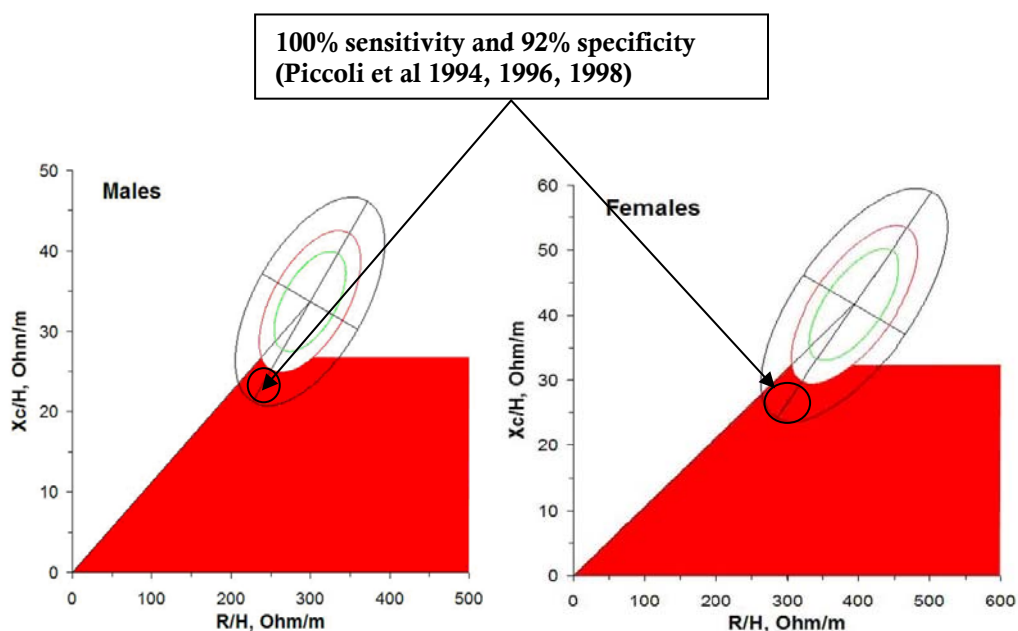
Figure 5.7 shows the individual vectors for all the patients analysed. In a sample of 46 patients defined as stable by medical doctors, 1 man and 0 women died. This represents 2.2% of the studied total. In the sample of 28 critical patients, 9 women and 11 men died, which represents 71.4% of the studied total. Analysis of the Z vector in the RXc plane is interesting since it provides information on the hydration state (R/H) and on the structure of soft tissues ( $X_c/H$ ) without having to assume a patient's dry weight. Statistical analysis, using Student's t test and Hotelling's  $T^2$  test, demonstrated that the parameters R/H,  $X_c/H$  and the phase angle were significantly different for both patient groups ( $P < 0.05$ ) (see Tables 5.5 and 5.6), and through Z-score for reference population in Figures 5.5. In Figure 5.6 we can see a graphic representation, through the 95% confidence ellipses of BIVA method, of the differences between the three components of the Z/H vector in both groups of patients.

In previous studies (Piccoli et al 96, 98), the inferior pole of the 75% tolerance ellipse was considered the threshold for oedema, as it obtained 100% sensitivity and 92% specificity (Piccoli et al. 1994, 1996 and 1998). If we use a similar criterion, defining as critical those patients outside the 75% tolerance ellipse and whose phase angles are lower than the mean vector phase angle we have the following results: twenty-two patients, diagnosed as stable by the clinic (10 women and 12 men), were hyperhydrated according to the BIVA method and no patient diagnosed as critical by the clinic was oedema-free according to the results of BIVA. The only stable patient died was not classified as stable by BIVA; the values for the Z/H vector for this patient indicated hyperhydration (Figure 5.7).

Phase angle was directly correlated with several parameters of nutritional state and independently associated with survival in hemodialysis patients (Chertow et al 1995, 1997). Phase angle and vector length, however, are geometrically linked and, independent of

nutritional state, a wider phase angle with longer vector length is observed in states of dehydration. In addition, new criteria based on the phase angle ( $\phi = \arctan \frac{X_c}{R}$ ) (Chertow 1996, Maggiore et al 1996) or using the component  $X_c$  (Ott et al 1995, Ikizler et al 1999) have been proposed.

The  $RX_c$ -graph area located outside the 75% tolerance ellipse, with phase angles lower than  $4^\circ$  for women and  $3.5^\circ$  for men (Table 5.3 and Table 5.4), appears to be the best threshold for survival ratio, with 100% sensitivity and 48% specificity (Figure 5.8). If we consider the separation, following the clinical criterion made by doctors, the sensitivity was 95% and the specificity 84%.



**Figure 5.8-** Critical zone in hard red with 100% sensitivity and 48% specificity

## 5.5 Conclusion

Some authors has shown that it is possible to obtain similar information at single frequency, for example at 50 kHz, and at multifrequency (Kuhlman et al 2005, Piccoli et al 2005-a, 2005-b). Taking into account the multifrequency errors we used the BIVA analysis at 50 kHz in HD patients.

Ikizler et al (1999) reported association of morbidity with markers of nutrition and inflammation in chronic hemodialysis patients in a prospective study. Our results demonstrate that there is a strong correlation between mortality and hyper-hydration (oedema) in patients undergoing periodic hemodialysis, due to risk of cardiac failure and

die present. Furthermore, the BIVA method could be used to detect hyper-hydration state before edema appears, and to predict survival through PA. Although we propose continuing to increase the sample size to confirm the statistical conclusions, BIVA could be a low-cost, non-invasive, objective and fast method to complement the clinical diagnosis and follow-up of HD patients. The follow-up of patients using the RXc-graph allows a better adjustment of dialysis sessions, diuretics, hypotensors and diet (Nescolarde et al 2001-a, 2002-a, 2002-b, 2003, and 2004-a, 2004-b).

## 5.6 References

- Bland JM, Altman DG (1999): Measuring agreement in method comparison studies. *Statistical Methods in Medical Research*, **8**:135-160.
- Bland JM, Altman DG (1986): Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet*, **1**:307-310.
- Cole KS (1940): Permeability and impermeability of cell membranes for ions. *Cold Spring Harbor Sympos Quant Biol*, **8**, 110-122.
- Cole KS (1932): Electrical phase angle of cell membranes. *J Gen Physiol*, **15**, 641-649.
- Cole KS (1928-b): Electrical impedance of suspensions of arbacia eggs. *J Gen Physiol*, **12**, 37-54.
- Cole KS (1928-a): Electrical impedance of suspensions of spheres. *J Gen Physiol*, **12**, 29-36.
- Cornish BH, Ward LC, Thomas BJ, Jebb SA, Elia M (1996): Evaluation of multiple frequency bioelectrical impedance and Cole-Cole analysis for the assessment of body water volumes in healthy humans. *Eur J Clin Nutr*, **50**:159-164.
- Cornish BH, Ward LC, Thomas BJ (1994): Alteration of the extracellular and total body water volumes measured by multiple frequency bioelectrical impedance analysis (MFBIA). *Nutr Research*, **14**(5):717-727.
- DiIorio BR, Scalfi L, Terracciano V, Bellizzi V (2004): A systematic evaluation of bioelectrical impedance measurement after hemodialysis session. *Kidney Int*, **65**:2435-2440.
- Ellis KJ (2000): Human body composition: in vivo methods. *Physiol Rev*, **80**:649-680.
- Ellis KJ, Bell SJ, Chertow GM, Chumlea WC (1999): Bioelectrical impedance methods in clinical research: A follow-up to the NIH technology assessment conference. *Nutrition*, **15** (11, 12): 874-880.
- Ellis KJ, Wong WW (1998): Human hydrometry: comparison of multifrequency bioelectrical impedance with deuterium and bromine dilution. *J Appl Physiol*, **85**:1056.
- Chertow GM, Jacobs DO, Lazarus JM, Lew NL, Lowrie EG (1997): Phase angle predicts survival in hemodialysis patients. *J Renal Nutr*, **7**:204.
- Chertow GM, Lowrie EG, Wilmore DW (1995): Nutritional assessment with bioelectrical impedance analysis in maintenance hemodialysis patients. *J Am Soc Neph*, **6**:75-81.
- Foster KR, Schwan HP (1996): Dielectric properties of tissues. *Handbook of Biological Effects of Electromagnetic Fields*, Chapter 1; 25-103.
- Grimnes S, Martinsen ØG (2005): Cole Electrical Impedance Model—A Critique and an Alternative. *IEEE Trans Biomed Eng*, **52**(1): 132-135
- Grimnes S, Martinsen ØG (2000): *Bioimpedance and bioelectricity basics*. London: Academic Press.
- Hanai T (1968): Electrical properties of emulsions. In: Sherman PH, ed. *Emulsion science*. London: Academic Press.
- Heymsfield SB, Wang ZM, Visser M (1996): Techniques used in the measurement of body composition: an overview with emphasis on bioelectrical impedance analysis. *Am J Clin Nutr*, **64**:478S-484S.
- Heymsfield SB, Wang ZM, Baumgartner RN, Ross R (1997): Human body composition: Advances in models and methods. *Annu Rev Nutr*, **17**:527-528.

- Hotelling, H (1947): Multivariate Quality Control. In C. Eisenhart, M. W. Hastay, and W. A. Wallis, eds. *Techniques of Statistical Analysis*. New York: McGraw-Hill.
- Houtkooper LB, Lohman TG, Going SB, Howell WH (1996): Why bioelectrical impedance analysis should be used for estimating adiposity. *Am J Clin Nutr*, **64**:436S-448S.
- Ikizler TA, Wingard RL, Harvell J (1999): Association of morbidity with markers of nutrition and inflammation in chronic hemodialysis patients: a prospective study. *Kidney Int*, **55**:1945-1951.
- Kuhlmann MK, Zhu F, Seibert E, Levin NW (2005): Bioimpedance, dry weight and blood pressure control: new methods and consequences. *Curr Opin Nephrol Hypertens*, **14**:543-549
- Lentner C (1982): Introduction to statistics. Statistical tables. Mathematical formulae, in Geigy Scientific Tables (vol 2, 8th ed), Basle, Ciba-Geigy Limited.
- Maggiore Q, Nigrelli S, Ciccarelli C (1996): Nutritional and prognostic correlates of bioimpedance indexes in hemodialysis patients. *Kidney Int*, **50**:2103-2108.
- Morrison DF (1967): Multivariate Statistical Methods. New York, MacGraw Hill.
- Nescolarde L, Piccoli A, Román A, Núñez A, Morales R, Tamayo J, Doñate T and Rosell J (2004): Bioelectrical impedance vector analysis in hemodialysis patients. Relation between oedema and mortality. *Physiol Meas*, **25**: 1271-1280.
- Nescolarde L, Piccoli A, Núñez A, Román A, Doñate T, Rosell J (2004): Análisis del vector impedancia eléctrica en pacientes sujetos a diálisis: edema, mortalidad y medidas segmentales. Proceedings of the *IV Jornades de Recerca en Enginyeria Biomèdica*, Barcelona (España). ISBN 84-688-6747-0 pp 131-136.
- Nescolarde L, Rosell J, Piccoli A, Román A, Núñez A, Morales R, Lara A (2004): Influence of race on impedance vector position in the R-Xc plane. Proceedings of the *XII International Conference on Electrical Bioimpedance*. Gdansk (Poland). ISBN-83-917681-6-3, pp 329-332.
- Nescolarde L, Piccoli A, Rosell J, Riu P (2003): Vector de distribución de impedancia eléctrica en pacientes con hemodiálisis periódica. Proceedings of the *V Congreso de la Sociedad Cubana de Bioingeniería*. Habana (Cuba). ISBN 959-212-055-1
- Nescolarde L, Piccoli A, Rosell J, Morales R (2002): Monitoring soft tissue hydration of hemodialysis patients with bivariate impedance vector analysis at 50 kHz and multifrequency analysis. Proceedings of the *2<sup>nd</sup> European Medical & Biological Engineering Conference*. Vienna (Austria). ISBN 3-901351-62-0, pp 122-123.
- Nescolarde L, Piccoli A, Rosell J, Bragos R (2002): Análisis vectorial de bioimpedancia eléctrica en pacientes con hemodiálisis periódica. Proceedings of the *Terceres Jornades de Recerca en Enginyeria Biomèdica*. Vic (España). ISBN 84-699-8705-5, pp 82-87.
- Nescolarde L, Lara A, Rosell J, Morales R (2001): Evaluation of the bioelectric parameters and their relationship with the distribution of liquids in patients with terminal chronic renal failure treated with periodic hemodialysis. *XI International Conference on Electrical Bioimpedance*. Oslo (Norway). ISBN 82- 91853- 05-3, pp 337-340.
- Nescolarde L, Lara A, Rosell J (2001): Evaluación de los parámetros bioeléctricos en una población adulta “sana”, escogida al azar, por el método de bioimpedancia. Estudio preliminar I. Proceedings of the *II Congreso Latinoamericano de Bioingeniería*. Habana (Cuba). ISBN 959- 7132- 57-5
- Piccoli A (2005): Whole Body-Single frequency bioimpedance. *Contrib Nephrol Basel Karger*, **49**: 150-161.

Piccoli A, Pastori G, Guizzo M (2005): Equivalence of information from single versus multiple frequency bioimpedance vector analysis in hemodialysis. *Kidney Int*, **67**:301-313.

Piccoli A for the Italian HD-BIA Study Group (2004): Bioimpedance vector migration up to three days after the hemodialysis session. *Kidney Int*, **66**:2088-2094.

Piccoli A, for the Italian CAPD-BIA study group (2004): Bioelectrical impedance vector distribution in peritoneal dialysis patients with different hydration state. *Kidney Int*, **65**:1050-1063.

Piccoli A, Pillon L, Dumler F (2002): Impedance vector distribution by sex, race, body mass index, and age in the United States: standard reference intervals as bivariate Z scores. *Nutrition*, **18**:153-167.

Piccoli A, Nescolarde L, Rosell J (2002): Análisis Convencional y Vectorial de Bioimpedancia en la Práctica Clínica. *Revista Española de Nefrología*, **XXII**: 230-240.

Piccoli A, Pastori G (2002): *BIVA software*. University of Padova.

Piccoli A, Pittoni G, Facco E (2000): Relationship between central venous pressure and bioimpedance vector analysis in critically ill patients. *Crit Care Med*, **28**:132-137.

Piccoli A, Pillon L, Tabbi MG (1999): Major confounders for reactance as a marker of malnutrition in hemodialysis patients. *Kidney Int*, **56**:2311-2312.

Piccoli A, Pillon L, Pisanello L (1999): Electrical maturation trajectory of human tissues identified by bioelectrical impedance vector analysis. *Nutrition*, **15**:77-78.

Piccoli A, Brunani A, Savia G (1998): Discriminating between body fat and fluid changes in the obese adult using bioimpedance vector analysis. *Int J Obesity*, **22**:97-104.

Piccoli A, for the Italian HD-BIA Study Group (1998): Identification of operational clues to dry weight prescription in hemodialysis using bioimpedance vector analysis. *Kidney Int*, **53**:1036-1043.

Piccoli A, Pillon L, Favaro E (1997): Asymmetry of the total body water prediction bias using the impedance index. *Nutrition*, **13**:438-441.

Piccoli A, Piazza P, Noventa D (1996): A new method for monitoring hydration at high altitude by bioimpedance analysis. *Med Sci Sports Exerc*, **28**:1517-1522.

Piccoli A, Rossi B, Pillon L (1996): Body fluid overload and bioelectrical impedance analysis in renal patients. *Miner Electrolyte Metab*, **22**:76-78.

Piccoli A, Nigrelli S, Caberlotto A, Bottazzo S, Rossi B, Pillon L, Maggiore Q (1995): Bivariate normal values of the bioelectrical impedance vector in adult and elderly populations. *Am J Clin Nutr*, **61**:269-270.

Piccoli A, Rossi B, Pillon L, Bucciantè G (1994): A new method for monitoring body fluid variation by bioimpedance analysis: The RXc graph. *Kidney Int*, **46**:534-539.

Piccoli A, Rossi B, Pillon L (1994): Operational equivalence between segmental and whole-body bioelectrical impedance in renal patients. *Am J Clin Nutr*, **59**:675-676

Pillon L, Piccoli A, Lowrie EG (2004): Vector length as a proxy for the adequacy of ultrafiltration in hemodialysis. *Kidney Int*, **66**:1266-1271.

Schwan HP (1957): Electrical properties of tissues and cell suspensions. In: Lawrence JH, Tobias CA (eds) *Advances in biological and medical physics*. Vol V, 147-209. Academic Press, New York.